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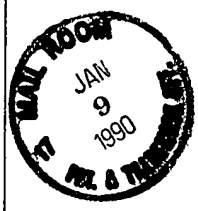

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CASE 4-16180/-/CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KNUT A. JAEGGI ET AL.

SERIAL NO: 315,962

FILED: FEBRUARY 27, 1989

FOR: NOVEL SUBSTITUTED ALKANE-DIPHOSPHONIC ACIDS

Group Art Unit: 121

Examiner: R. Schwartz

Commissioner of Patents and Trademarks

Washington, D.C. 20231

CLAIM OF PRIORITY UNDER 35 USC 119

Sir:

Applicants in the above-entitled application by their attorney hereby claim priority under the International Convention of Swiss application No. 04 666/86-0, filed on November 21, 1986. This application is acknowledged in the Declaration of the instant case.

A certified copy of said Swiss application is submitted herewith.

Respectfully submitted,

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Encl. (1)

#5

Swiss Confederation
Certificate

The accompanying documents agree with the original technical supporting documents of the Patent Application for Switzerland and Liechtenstein* named on the following page.

Bern, 25th Sep. 1987

Seal of the Federal Office
for Intellectual Property

Federal Office for
Intellectual Property

Head of Section

(signature)

Grünig

*Switzerland and the Principality of Liechtenstein form a single area of protection. Protection can therefore be requested only for the two countries jointly.

Probable class(es): C07F/A61K Patent Application No. 04 666/86-0

Patent
Applicant: CIBA-GEIGY AG
4002 Basle
Switzerland

Title: Novel substituted alkanediphosphonic acids.

Date of
application: 21.11.86

Priority: -

Reference: 4-16180

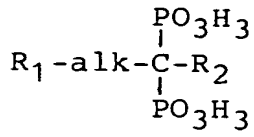
Unalterable copy

CIBA-GEIGY AG
Basle (Switzerland)

4-16180
Switzerland

Novel substituted alkanediphosphonic acids

The present invention relates to novel substituted alkanediphosphonic acids, especially heteroarylalkanediphosphonic acids of formula



wherein R_1 is an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atoms, 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom, and that is unsubstituted or is C-substituted by lower alkyl, phenyl or phenyl that is substituted by lower alkyl, lower alkoxy and/or halogen, or by lower alkoxy, hydroxy, di-lower alkylamino, lower alkylthio and/or by halogen, and/or is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and to the salts thereof, to processes for the preparation of the compounds according to the invention, to pharmaceutical compositions containing them, and to the use thereof as active ingredients in medicaments.

Examples of optionally benzo- or cyclohexeno-fused

5-membered heteroaryl radicals containing 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom as hetero atoms are: imidozolyl, e.g. imidazol-1-yl, imidazol-2-yl or imidazol-4-yl, pyrazolyl, e.g. pyrazol-1-yl or pyrazol-3-yl, thiazolyl, e.g. thiazol-2-yl or thiazol-4-yl, or, less preferably, oxazolyl, e.g. oxazol-2-yl or oxazol-4-yl, isoxazolyl, e.g. isoxazol-3-yl or isoxazol-4-yl, triazolyl, e.g. 4H-,1,2,4-triazol-3-yl, 4H-1,2,4-triazol-4-yl or 2H-1,2,3-triazol-4-yl, tetrazolyl, e.g. tetrazol-5-yl, thiadiazolyl, e.g. 1,2,5-thiadiazol-3-yl, oxadiazolyl, e.g. 1,3,4-oxadiazol-2-yl, benzimidazolyl, e.g. benzimidazol-2-yl, benzoxazolyl, e.g. benzoxazol-2-yl, or benzothiazolyl, e.g. benzothiazol-2-yl. These radicals may contain one or more identical or different, especially one or two identical or different, substituents selected from those mentioned at the beginning.

Radicals and compounds hereinafter qualified by the term "lower" shall be understood as meaning, for example, those containing up to and including 7 carbon atoms, especially up to and including 4 carbon atoms. The general terms have, for example, the following meanings:

Lower alkoxy is, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy or tert.-butoxy.

Di-lower alkylamino is, for example, di-C_1-C_4-alkylamino, such as dimethylamino, diethylamino, N-ethyl-N-methylamino, dipropylamino, N-methyl-N-propylamino or dibutylamino.

Lower alkylthio is, for example, C_1-C_4-alkylthio, such as methylthio, ethylthio, propylthio or butylthio, and also isobutylthio, sec.-butylthio or tert.-butylthio.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as fluorine,

chlorine or bromine.

Lower alkylene is, for example, C_1-C_4-alkylene, such as especially methylene, and also ethylene or 1,3-propylene.

Salts of compounds of formula I are especially the salts thereof with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, e.g. alkali metals, especially sodium or potassium salts, alkaline earth metal salts, especially calcium or magnesium salts, copper, aluminium or zinc salts, and also ammonium salts with ammonia or organic amines or quaternary ammonium bases, such as optionally C-hydroxylated aliphatic amines, especially mono-, di- or tri-lower alkylamines, e.g. methylamine, ethylamine, dimethylamine or diethylamine, mono-, di- or tri-(hydroxy-lower alkyl)-amines, such as ethanolamine, diethanolamine or triethanolamine, tris(hydroxymethyl)aminomethane or 2-hydroxy-tert.-butylamine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkylamines and N-(polyhydroxy-lower alkyl)-N-lower alkylamines, such as 2-(dimethylamino)ethanol or D-glucamine, or quaternary aliphatic ammonium hydroxides, e.g. with tetrabutylammonium hydroxide.

In this connection it should also be mentioned that the compounds of formula I may also be in the form of internal salts, provided the group R_1 is sufficiently basic. These compounds can therefore also be converted into the corresponding acid addition salts by treatment with a strong protonic acid, such as a hydrohalic acid, sulphuric acid, sulphonic acid, e.g. methanesulphonic acid or p-toluenesulphonic acid, or sulphamic acid, e.g. N-cyclohexylsulphamic acid.

The compounds of formula I and salts thereof have valuable pharmacological properties. In particular, they have a pronounced regulatory action on the calcium metabolism of warm-blooded animals. In particular, they

effect a marked inhibition of bone resorption in rats, as can be demonstrated in the experimental procedure described in Acta. Endocrinol. 78, 613-24 (1975) both by means of the PTH-induced increase in the serum calcium level after subcutaneous administration of doses in the range of from about 0.01 to about 1.0 mg/kg, and also after administration of vitamin D_3 metabolites in doses of from about 0.001 to about 1.0 mg/kg. Tumour hypercalcaemia induced by Walker 256 tumours is likewise inhibited after peroral administration of about 1.0 to 100 mg/kg. In addition, when administered subcutaneously in a dosage of about 0.01 to 1.0 mg/kg in the experimental procedure of N. Kaibara et al., J. Exp. Med. 159, 1388-96 (1984), they exhibit a marked inhibition of the progression of chronic arthritic conditions in rats with adjuvant arthritis. They are therefore eminently suitable as active ingredients in medicaments for the treatment of diseases that are associated with disorders of the calcium metabolism. Favourable results are achieved in the treatment of diseases in which an abnormal deposit of poorly soluble calcium salts is observed, for example in the case of calcium deposits in blood vessels or on prosthetic implants, such as in arthritic diseases, e.g. ankylosing spondilitis, neuritis, bursitis and tendinitis, fibrodysplasia, osteoarthrosis or arteriosclerosis, and also in those diseases in which an abnormal decomposition of hard body tissue is the principal symptom, such as hereditary hypophosphatasia, osteoporoses of various origins, Paget's disease and osteodystrophia fibrosa, and also osteolytic conditions induced by tumours.

The invention relates especially to compounds of formula I wherein R_1 is an imidazolyl, benzimidazolyl, pyrazolyl, 2H-1,2,3-triazolyl or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, benzothiazolyl or thiadiazolyl

radical that is unsubstituted or is C-substituted by one or two substituents selected from lower alkyl, lower alkoxy, phenyl or phenyl that is substituted by one or two substituents selected from lower alkyl, lower alkoxy and/or halogen, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by one or two substituents selected from lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, especially the internal salts and pharmaceutically acceptable salts thereof with bases.

The invention relates more especially to compounds of formula I wherein R_1 is an imidazolyl radical, such as imidazol-1-yl, imidazol-2-yl or imidazol-4-yl, a 4H-1,2,4-triazolyl radical, such as 4H-1,2,4-triazol-4-yl, a thiazolyl radical, such as thiazol-2-yl, or a benzimidazolyl radical, such as benzimidazol-2-yl, each of which radicals is unsubstituted or is C-substituted by one or two substituents selected from C_1-C_4-alkyl, such as methyl, C_1-C_4-alkoxy, such as methoxy, phenyl, hydroxy, di-C_1-C_4-alkylamino, such as dimethylamino or diethylamino, C_1-C_4-alkylthio, such as methylthio, and/or halogen having an atomic number of up to and including 35, such as chlorine, and/or is N-substituted by C_1-C_4-alkyl, such as methyl, or by phenyl-C_1-C_4-alkyl, such as benzyl, alk* is C_1-C_4-alkylene, such as methylene, and R_2 is especially hydroxy or, less preferably, hydrogen or amino, and salts thereof, especially the internal salts and pharmaceutically acceptable salts thereof with bases.

The invention relates specifically to the compounds of formula I mentioned in the Examples and to the salts

*Translator's note: It is assumed that "alk" was inadvertently omitted from the German text.

thereof, especially the internal salts and pharmaceutically acceptable salts thereof with bases.

The invention further relates to a process based on per se known methods for the preparation of compounds of formula I and salts thereof. This process is characterised in that

a) in a compound of formula

$$R_1 - alk - \overset{\overset{X_1}{|}}{\underset{\underset{X_2}{|}}{C}} - R_2 \qquad (II),$$

wherein X_1 is a functionally modified phosphono group and X_2 is a free or functionally modified phosphono group, X_1 and, if appropriate, X_2 is (are) converted into the free phosphono group, or

b) a compound of formula

$$R - alk - X_3 \qquad (III),$$

wherein X_3 is carboxy or cyano, is reacted with phosphorous acid and phosphorus trichloride, and, where compounds of formula IV wherein X_3 is cyano are used as starting material, compounds of formula I wherein R_2 is amino are obtained, and, if desired, a resulting compound is converted into another compound of formula I and/or a resulting free compound is converted into a salt or a resulting salt is converted into the free compound or into another salt.

In process variant a), functionally modified phosphono groups that are to be converted into phosphono are, for example, in ester form, especially in a diester form of formula $-P(=O)(OR)_2$ (IV) wherein OR is, for

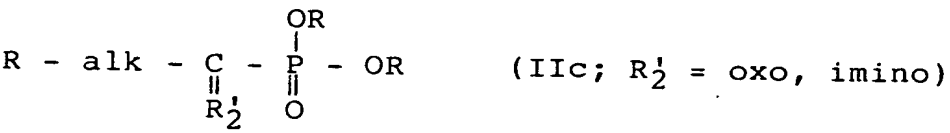
example, lower alkoxy or a phenoxy group that is unsubstituted or is substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl and/or by hydroxy.

The conversion of a functionally modified phosphono group into the free phosphono group is effected in conventional manner by hydrolysis, for example in the presence of a mineral acid, such as hydrobromic acid, hydrochloric acid or sulphuric acid, or by reaction with a tri-lower alkylhalosilane, for example with trimethyldichlorosilane, or especially with trimethyliodosilane or trimethylbromosilane, preferably while cooling, for example in a temperature range of from about 0° to about 25°C.

The starting materials of formula II wherein R_2 is hydroxy or amino can be prepared, for example, by reacting a compound of formula

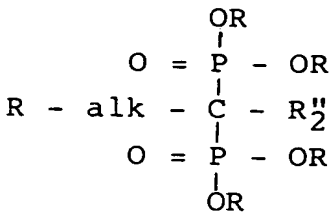
$$R - alk - COOH \qquad (IIa),$$

or preferably the nitrile or acid chloride thereof, with a suitable phosphorous acid triester of formula $P(OR)_3$ (IIb) wherein R is, for example, lower alkyl, in the presence of tri-lower alkylamine, for example triethylamine, to give a compound of formula



(IIc; R_2' = oxo, imino)

and subsequently reacting the latter compound with a phosphorous acid diester of formula $H-P(=O)(OR)_2$ (IId) or $P(OH)(OR)_2$ (IIe) wherein R is, for example, lower alkyl, in the presence of a di-lower alkylamino, for example diethylamine, or of an alkali metal lower alkanolate, for example sodium methanolate, to give the corresponding compound of formula

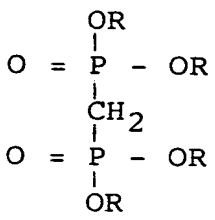


(IIf; R''_2 = hydroxy, amino).

Starting materials II wherein R_2 is hydrogen are obtained, for example, by reacting a compound of formula

R-alk-Y (IIg)

wherein Y is reactive esterified hydroxy, especially halogen, such as bromine, in the presence of a metal base, such as the hydride, an amide or a hydrocarbon compound of an alkali metal, e.g. sodium hydride, sodium amide, ditrimethylsilyl sodium amide or butyllithium, with a methane diphosphonate, e.g. of formula



(IIh)

wherein R is, for example, lower alkyl.

Compounds of formula II wherein R_2 is lower alkylthio or halogen can be prepared, for example, starting from corresponding compounds II wherein R_2 is hydrogen, by converting these with a strong base, for example one of those mentioned above, into the carbeniate salt and subsequently reacting said salt with a lower alkylthio donor, for example a di-lower alkyl disulphite or a lower alkanesulphonyl chloride, or with a halogen donor, for example a halogen, e.g. chlorine or bromine, perchloryl fluoride ($FClO_3$) or the like.

The reaction of compounds of formula III with phosphorous acid and phosphorus trichloride according to process variant b) is carried out in conventional manner, advantageously while heating, for example to about 70° to 120°C, in a suitable solvent, such as tetrachloroethane, trichloroethane, chlorobenzene, chlorotoluene or paraffin oil, and with working up by hydrolysis.

The starting materials of formula III, if not known, can be prepared, for example, by converting an appropriate compound of formula

$$Y_1 - CH_3 \qquad \text{(IIIa)}$$

with a strong base, for example with one of the metal bases mentioned in process variant a), into the carbeniate salt and reacting said salt with carbon dioxide or with a cyanogen halide, such as cyanogen chloride.

Compounds of formula I obtained by the process of this invention or by other per se known processes can be converted into other compounds of formula I in a manner known per se.

Thus, for example, compounds of formula I wherein R_2 is amino can be converted by treatment with nitrous acid into the corresponding compounds of formula I wherein R_2 is hydroxy. The treatment with nitrous acid is effected in conventional manner with formation of same in aqueous solution from a salt thereof, for example from sodium nitrite, by treatment with an acid, for example hydrochloric acid, to form a corresponding unstable diazonium salt as intermediate, for example diazonium chloride, which splits off nitrogen upon introduction of the α-hydroxy group.

Depending on the starting materials and procedures chosen, the novel compounds may be in the form of one of

the possible isomers or in the form of a mixture thereof, for example depending on the number of asymmetric carbon atoms, in the form of pure optical isomers, such as antipodes, or in the form of isomeric mixtures, such as racemates, diastereoisomeric mixtures or mixtures of racemates.

Resulting diastereoisomeric mixtures and mixtures of racemates can be separated in known manner into the pure isomers, diastereoisomers or racemates on the basis of the physico-chemical differences between the components, for example by chromatography and/or fractional crystallisation.

Resulting racemates can further be resolved into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of microorganisms, or by reacting an acid end product with an optically active base that forms salts with the racemic acid and separating the resulting salts in known manner, for example on the basis of their different solubilities, into the diastereoisomers from which the antipodes can be freed by the action of suitable agents. Advantageously, the more active of the two antipodes is isolated.

Resulting free compounds of formula I, including the internal salts thereof of formula I, can be converted into basic salts by partial or complete neutralisation with one of the bases mentioned at the beginning. Analogously, it is also possible to convert acid addition salts into the corresponding free compounds or their internal salts.

Conversely, resulting free compounds of formula I can be converted into acid addition salts of formula I" by treatment with one of the protonic acids mentioned at the beginning.

Resulting salts can be converted in a manner known per se into the free compounds, for example by

treatment with an acid reagent, such as a mineral acid, or a base, for example an alkali metal hydroxide solution.

The compounds, including their salts, can also be obtained in the form of hydrates or may contain the solvent used for crystallisation.

Because of the close relationship between the novel compounds in the free form and in the form of their salts, the references made throughout this specification to the free compounds and their salts may also apply by analogy to the corresponding salts and the free compounds, respectively.

The invention also relates to those embodiments of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or a starting material is used in the form of a salt and/or racemate or antipode, or, especially, is formed under the reaction conditions.

In the process of this invention it is preferred to use those starting materials that result in the compounds described at the beginning as being especially valuable. The invention relates also to novel starting materials and processes for the preparation thereof.

The pharmaceutical compositions according to the invention, which contain compounds of formula I or pharmaceutically acceptable thereof, are those for enteral, such as oral or rectal, and parenteral administration, the pharmacological active ingredient being present alone or together with a pharmaceutically suitable carrier. The dosage of the active ingredient depends on the species of warm-blooded animal, its age and individual condition and on the mode of administration. The normal daily dose recommended for a warm-blooded animal weighing approximately 75 kg is approximately from 30 to 1000 mg, preferably approx-

imately from 100 to 1000 mg, and, in the case of intravenous administration, approximately from 1 to 50 mg, preferably approximately from 5 to 30 mg, advantageously divided into several equal partial doses.

The novel pharmaceutical compositions contain, for example, from about 10% to about 80%, preferably from about 20% to about 60%, active ingredient. Pharmaceutical compositions according to the invention for enteral or parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets, capsules or suppositories, and also ampoules. These pharmaceutical compositions are prepared in a manner known per se, for example by conventional mixing, granulating, confectioning, dissolving or lyophilising methods. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable excipients, to tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, e.g. lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, e.g. maize, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow-regulating agents and lubricants, for example silica, talcum, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which may be resistant to gastric

juices, using inter alia concentrated sugar solutions which may contain gum arabic, talcum, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or mixtures of solvents or, for the preparation of coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example to identify or indicate different doses of active ingredient.

Further pharmaceutical compositions for oral administration are dry-filled capsules made of gelatin and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talcum or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in a suitable liquid, such as a fatty oil, paraffin oil or a liquid polyethylene glycol, to which a stabiliser can also be added.

Suitable pharmaceutical compositions for rectal administration are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Examples of suitable suppository bases are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules which contain a combination of the active ingredient with a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

Particularly suitable dosage forms for parenteral

administration are aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, for which there are used suitable lipophilic solvents or vehicles, such as fatty oils, e.g. sesame oil, or synthetic fatty acid esters, e.g. ethyl oleate or triglycerides, or aqueous injection suspensions which contain substances that increase the viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also stabilisers.

The present invention also relates to the use of the compounds of formula I and salts thereof, preferably for the treatment of inflammatory conditions, primarily for diseases associated with disorders of the calcium metabolism, e.g. rheumatic diseases and, in particular, osteoporoses.

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope thereof in any way. Temperatures are given in degrees Celsius.

Example 1: With stirring and under reflux, 8.6 g (0.053 mole) of imidazol-4-ylacetic acid hydrochloride, 7.1 ml of 85% phosphoric acid and 25 ml of chlorobenzene are heated to 100°. Then 13.9 ml of phosphorus trichloride are added dropwise at 100°, whereupon evolution of gas occurs. Over the course of 30 minutes a thick mass separates from the reaction mixture. The batch is heated for a further 3 hours at 100° and the supernatant chlorobenzene is then removed by decanting. With stirring and under reflux, the viscous mass remaining is heated at the boil for 3 hours with 40 ml of 9N hydrochloric acid. The batch is filtered hot with the addition of carbon and the filtrate is diluted with

acetone, whereupon the crude 2-(imidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid separates. This product is recrystallised from water. Melting point: 238-240° (decomp.). (Yield: 41% of the theoretical yield).

Example 2: With stirring and under reflux, 15.7 g (0.1 mole) of benzimidazol-2-ylacetonitrile, 13.4 ml of 85% phosphoric acid and 50 ml of chlorobenzene are heated to 100°. Then 27 ml of phosphorus trichloride are added dropwise at 100°, whereupon evolution of gas occurs. Over the course of 30 minutes a thick mass separates from the reaction mixture. The batch is heated for a further 3 hours at 100° and the supernatant chlorobenzene is then removed by decanting. With stirring and under reflux, the viscous mass remaining is heated at the boil for 3 hours with 100 ml of 9N hydrochloric acid. The batch is filtered hot with the addition of carbon and the filtrate is cooled, whereupon 1-amino-2-(1-benzimidazol-2-yl)-ethane-1,1-diphosphonic acid separates in crystalline form. M.p. 290-292° (decomp.). (Yield: 8% of the theoretical yield).

Example 3: 3.8 g (0.012 mole) of 1-amino-2-(2-benzimidazolyl)-ethane-1,1-diphosphonic acid are introduced in portions into a cooled sodium nitrite solution that has been adjusted to pH 2 with hydrochloric acid. The batch is then stirred for 12 hours while cooling with ice, the resulting suspension is filtered with suction and the precipitate is washed with water and methanol. In this manner, 2-(2-benzimidazolyl)-1-hydroxy-ethane-1,1-diphosphonic acid of m.p. 212°C (decomp.) is obtained. (Yield: 47%).

Example 4: In a manner analogous to that described in Example 1 and starting from 0.05 mole in each case of

(1-methylimidazol-2-yl)acetic acid,
(1-benzylimidazol-2-yl)acetic acid,
(1-methylimidazol-4-yl)acetic acid,
imidazol-1-ylacetic acid and
4H-1,2,4-triazol-4-ylacetic acid,
the following compounds are respectively obtained:
2-(1-methylimidazol-2-yl)-1-hydroxy-ethane-1,1-diphosphonic acid,
2-(1-benzylimidazol-2-yl)-1-hydroxy-ethane-1,1-diphosphonic acid,
2-(1-methylimidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid,
2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-bisphonic acid and
2-(4H-1,2,4-triazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid,
and the salts thereof, for example the disodium salts.

Example 5: In a manner analogous to that described in Example 2 and starting from 0.1 mole in each case of
(1-methylimidazol-4-yl)acetonitrile and
(1-benzylimidazol-4-yl)acetonitrile,
there are also obtained
1-amino-2-(1-methylimidazol-4-yl)-ethane-1,1-diphosphonic acid and
1-amino-2-(1-benzylimidazol-4-yl)-ethane-1,1-diphosphonic acid, respectively,
and the salts thereof, for example the disodium salts.

Example 6: In a manner known per se, for example by reaction of 1-methylimidazol-2-ylmethyl bromide, benzimidazol-2-ylmethyl chloride, p-toluenesulphonic acid (imidazol-1-ylmethyl) ester, imidazol-4-ylmethyl chloride and thiazolyl-2-ylmethyl bromide with methanediphosphonic acid tetraethyl ester and hydrolysis of the initially obtained ethanediphosphonic acid ester

analogously to Example 1 or 2, it is also possible to prepare
2-(1-methylimidazol-2-yl)ethane-1,1-diphosphonic acid,
2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid,
2-(imidazol-1-yl)ethane-1,1-diphosphonic acid,
2-(imidazol-4-yl)ethane-1,1-diphosphonic acid, and
2-(thiazol-2-yl)ethane-1,1-diphosphonic acid,
and the salts thereof, for example the disodium salts.

Example 7: Tablets, each containing 25 mg of active ingredient, e.g. 2-(imidazol-4-yl)ethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 1000 tablets)

active ingredient	25.0 g
lactose	100.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talcum	5.0 g
magnesium stearate	1.8 g
demineralised water	q.s.

Procedure: All the solid constituents are first forced through a sieve having a mesh size of 0.6 mm. The active ingredient is then mixed with the lactose, talcum, magnesium stearate and half of the starch. The other half of the starch is suspended in 40 ml of water and the suspension is added to a boiling solution of polyethylene glycol in 100 ml of water, and the mixture is granulated, if necessary with the further addition of water. The granulate is dried overnight at 35°, forced through a sieve having a mesh size of 1.2 mm, and compressed to tablets of about 6 mm diameter which are concave on both sides.

In an analogous manner, tablets each containing

25 mg of another compound of formula I mentioned in Examples 1 to 6 can also be prepared, which compounds may also be in the form of salts with bases, e.g. the sodium salt.

Example 8: Lozenges, each containing 30 mg of active ingredient, e.g. 2-(imidazol-4-yl)ethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 1000 tablets)

active ingredient	30.0 g
mannitol	267.0 g
lactose	179.5 g
talcum	20.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.0 g
5% gelatin solution	q.s.

Procedure: All the solid ingredients are first forced through a sieve having a mesh size of 0.25 mm. The mannitol and the lactose are mixed, the mixture is granulated while adding gelatin solution, forced through a sieve having a mesh size of 2 mm, dried at 50° and once more forced through a sieve having a mesh size of 1.7 mm. The active ingredient, glycine and saccharin are carefully mixed, then the mannitol, lactose granulate, stearic acid and the talcum are added. All the ingredients are thoroughly mixed and compressed to tablets having a diameter of about 10 mm which are concave on both sides and provided with a breaking groove on the upper side.

In an analogous manner, tablets each containing 30 mg of another compound of formula I mentioned in Examples 1 to 6 can also be prepared, which compounds

may also be in the form of salts with bases, e.g. the sodium salt.

Example 9: Tablets, each containing 100 mg of active ingredient, e.g. 1-(imidazol-4-yl)ethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 1000 tablets)

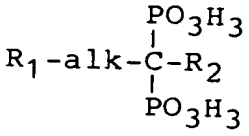
active ingredient	100.0 g
lactose	248.5 g
maize starch	17.5 g
polyethylene glycol 6000	5.0 g
talcum	15.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

Procedure: The solid constituents are first forced through a sieve having a mesh size of 0.6 mm. The active ingredient is then intimately mixed with the lactose, talcum, magnesium stearate and half of the starch. The other half of the starch is suspended in 65 ml of water and the suspension is added to a boiling solution of polyethylene glycol in 260 ml of water. The resulting paste is added to the powder substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°, forced through a sieve having a mesh size of 1.2 mm, and compressed to tablets of about 10 mm diameter which are concave on both sides and provided with a breaking notch on the upper side.

In an analogous manner, tablets each containing 100 mg of another compound of formula I mentioned in Examples 1 to 6 can also be prepared, which compounds may also be in the form of salts with bases, e.g. the sodium salt.

Patent Claims

1. Substituted alkanediphosphonic acids, especially heteroarylalkanediphosphonic acids of formula



wherein R_1 is an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atoms, 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom, and that is unsubstituted or is C-substituted by lower alkyl, phenyl or phenyl that is substituted by lower alkyl, lower alkoxy and/or halogen, or by lower alkoxy, hydroxy, di-lower alkylamino, lower alkylthio and/or by halogen, and/or is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof.

2. Compounds of formula I wherein R_1 is an imidazolyl, benzimidazolyl, pyrazolyl, 2H-1,2,3-triazolyl or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, benzothiazolyl or thiadiazolyl radical that is unsubstituted or is C-substituted by one or two substituents selected from lower alkyl, lower alkoxy, phenyl or phenyl that is substituted by one or two substituents selected from lower alkyl, lower alkoxy and/or halogen, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted by lower alkyl or by phenyl-lower

alkyl that is unsubstituted or is substituted by one or two substituents selected from lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof.

3. Compounds of formula I wherein R_1 is an imidazolyl, 4H-1,2,4-triazolyl, thiazolyl or benzimidazolyl radical that is unsubstituted or is C-substituted by one or two substituents selected from C_1-C_4-alkyl, C_1-C_4-alkoxy, phenyl, hydroxy, di-C_1-C_4-alkylamino, C_1-C_4-alkylthio, and/or halogen having an atomic number of up to and including 35, and/or is N-substituted by C_1-C_4-alkyl or by phenyl-C_1-C_4-alkyl, alk* is C_1-C_4-alkylene, and R_2 is hydroxy, hydrogen or amino, and salts thereof.

4. 2-(imidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid or a salt thereof.

5. 1-amino-2-(benzimidazol-2-yl)-ethane-1,1-diphosphonic acid or a salt thereof.

6. 2-(2-benzimidazolyl)-1-hydroxy-ethane-1,1-diphosphonic acid or a salt thereof.

7. 2-(1-methylimidazol-2-yl)-1-hydroxy-ethane-1,1-diphosphonic acid, 2-(1-benzylimidazol-2-yl)-1-hydroxy-ethane-1,1-diphosphonic acid, 2-(1-methylimidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid, 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-bisphonic acid or 2-(4H-1,2,4-triazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid or a salt thereof in each case.

*Translator's note: It is assumed that "alk" was inadvertently omitted from the German text.

8. 1-amino-2-(1-methylimidazol-4-yl)-ethane-1,1-diphosphonic acid or 1-amino-2-(1-benzylimidazol-4-yl)-ethane-1,1-diphosphonic acid or a salt thereof in each case.

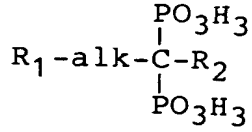
9. 2-(1-methylimidazol-2-yl)ethane-1,1-diphosphonic acid, 2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid, 2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, 2-(imidazol-4-yl)ethane-1,1-diphosphonic acid or 2-(thiazol-2-yl)ethane-1,1-diphosphonic acid or a salt thereof in each case.

10. A compound according to any one of claims 1 to 9 for use in a method for the therapeutic treatment of the human or animal body.

11. A compound according to any one of claims 1 to 9 as an agent that regulates calcium metabolism and/or as an anti-arthritic agent.

12. Pharmaceutical compositions containing a compound according to any one of claims 1 to 11 together with conventional pharmaceutical adjuncts.

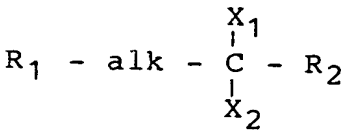
13. A process for the preparation of alkanediphosphonic acids, especially heteroarylalkanediphosphonic acids of formula



wherein R_1 is an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atoms, 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom, and that is unsubstituted or is

C-substituted by lower alkyl, phenyl or phenyl that is substituted by lower alkyl, lower alkoxy and/or halogen, or by lower alkoxy, hydroxy, di-lower alkylamino, lower alkylthio and/or by halogen, and/or is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, characterised in that

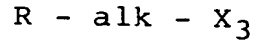
a) in a compound of formula



(II),

wherein X_1 is a functionally modified phosphono group and X_2 is a free or functionally modified phosphono group, X_1 and, if appropriate, X_2 is (are) converted into the free phosphono group, or

b) a compound of formula



(III),

wherein X_3 is carboxy or cyano, is reacted with phosphorous acid and phosphorus trichloride, and, where compounds of formula IV wherein X_3 is cyano are used as starting material, compounds of formula I wherein R_2 is amino are obtained, and, if desired, a resulting compound is converted into another compound of formula I and/or a resulting free compound is converted into a salt or a resulting salt is converted into the free compound or into another salt.

14. A process according to claim 13, characterised in that a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or a starting material is used in the form of a salt and/or racemate or antipode, or, especially, is formed under the reaction conditions.

15. The process of Examples 1 to 6.

16. The novel starting materials used, novel intermediates formed and novel end products obtainable in the process according to any one of claims 13 to 15.

17. The use of a compound according to any one of claims 1 to 11 for the treatment of calcium metabolism diseases.

18. A method for the treatment of calcium metabolism diseases, characterised in that a compound according to any one of claims 1 to 11 or a pharmaceutical composition according to claim 12 is administered.

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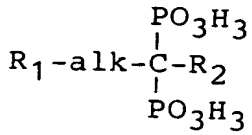
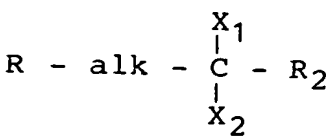
Novel substituted alkanediphosphonic acids

Abstract

Alkanediphosphonic acids, especially heteroaryl-alkanediphosphonic acids of formula



wherein R_1 is an optionally benzo- or cyclohexeno-fused 5-membered heteroaryl radical that contains, as hetero atoms, 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom, and that is unsubstituted or is C-substituted by lower alkyl, phenyl or phenyl that is substituted by lower alkyl, lower alkoxy and/or halogen, or by lower alkoxy, hydroxy, di-lower alkylamino, lower alkylthio and/or by halogen, and/or is N-substituted by lower alkyl or by phenyl-lower alkyl that is unsubstituted or is substituted by lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, have regulatory properties on calcium metabolism and can be used as medicaments for the treatment of diseases associated with calcium metabolism disorders. They are prepared, for example, as follows: in a compound of formula



(II),

wherein X_1 is a functionally modified phosphono group

and X_2 is a free or functionally modified phosphono group, X_1 and, if appropriate, X_2 is (are) converted into the free phosphono group.